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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/869,406	06/05/1997	WOLFGANG BARNIKOL	DT-2179	5708

30377 7590 02/12/2004

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EXAMINER	
GUPTA, ANISH	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 02/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 103

Application Number: 08/869,406
Filing Date: June 05, 1997
Appellant(s): BARNIKOL, WOLFGANG

Mail 02-19-04

David Toren
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10-09-03.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 6-9 and 11-15 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

4,136,093 Bonhard et al. 1-1979

Potzschke et al., 'A NEW TYPE OF ARTIFICIAL OXYGEN CARRIER, SOLUBLE HYPERPOLYMERIC HAEMOGLOBIN WITH NEGLIGIBLE ONCOTIC PRESSURE-

PRODUCTION OF THEREMALLY STABLE HYPERPOLYUMERS FROM HUMAN BLOOD WITH GLUTERALDEHYDE AS CROSS-LINKER," Biomat., Art. Cells & Immob. Biotech., Vol. 20 (2-4) (1992), pp. 287-291.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6-9 and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Potzschke et al.

The claims are drawn to a method of preparing molecularly uniform hyperpolymeric hemoglobins from a solution containing only cross-linked hyperpolymeric hemoglobin molecules with a size which is up to (5-10) x 100 times a size of quaternary hemoglobin molecules. The method involves performing at least one method step cited in the claims.

The reference or Potzschke et al. teaches the crosslinking of hemoglobin with glutaraldehyde and then purifying the product with sephaacryl s-400 high resolution gel (see Materials and Methods). The reference specifically states that the hemoglobin was first crosslinked using gluteraldehyde or 1, 4 cyclohexylene-diisocyanate to obtain crosslinked hyperpolymers (see page 289.) Note that the use of gluteraldehyde meets the limitation of claim 8 which recites

gluteraldehyde as the cross-linking agent. The reference further states that the crosslinked hemoglobin hyperpolymers are subject to a HEPES buffer solution to reduce the hyperpolymer solution (see page 289). This specification of the instant application utilizes the same procedure to crosslink the hemoglobin, specifically citing the Potzschke reference (see page 12-15 of the specification). Finally, the reference states that the solution is applied to gel chromatography, wherein the gel is a Sephacryl S-400 high resolution gel and the buffer contains 144 mmol/l of NaCl, 10mmol/L of Hepes buffer, and 3 mmol/l of NaN3. Note that this is the same gel and buffer solution is claimed in claim 9. The reference also states that all of the hyperpolyemric hemoglobin obtained were well fractionable in ultrafiltration (see page 290). Given that the method utilized for cross-linking is the for both the reference and the instant application and given that the purification procedure utilizes the same purification gel and the same buffer, the molecular weight achieved would necessarily be between (5-10) x 100 times the size of native hemoglobin. It should be noted that the reference states that the molecular weight of the hemoglobin was "very high." (See page 290). The reference anticipates the claimed invention because the reference specifically teaches "at least one" of the steps that are claimed in claim 6 and 11, namely the chromatographic fractionation with Sephacryl-400.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Potzschke et al.

The claims are drawn to a method of preparing molecularly uniform hyperpolymeric hemoglobins from a solution containing only cross-linked hyperpolymeric hemoglobin molecules with a size which is up to (5-10) x 100 times a size of quaternary hemoglobin molecules. The method involves performing at least one method step cited in the claims.

The reference or Potzschke et al. teaches the crosslinking of hemoglobin with glutaraldehyde and then purifying the product with sephaacryl s-400 high resolution gel (see Materials and Methods). The reference specifically states that the hemoglobin was first crosslinked using gluteraldehyde or 1, 4 cyclohexylene-diisocyanate to obtain crosslinked hyperpolymers (see page 289.) Note that the use of gluteraldehyde meets the limitation of claim 8 which recites gluteraldehyde as the cross-linking agent. The reference further states that the crosslinked hemoglobin hyperpolymers are subject to a HEPES buffer solution to reduce the hyperpolymer solution (see page 289). This specification of the instant application utilizes the same procedure to crosslink the hemoglobin, specifically citing the Potzschke reference (see page 12-15 of the specification). Finally, the reference states that the solution is applied to gel chromatography,

wherein the gel is a Sephacryl S-400 high resolution gel and the buffer contains 144 mmol/l of NaCl, 10mmol/L of Hepes buffer, and 3 mmol/l of NaN3. Note that this is the same gel and buffer solution as is claimed in claim 9. The reference also states that all of the hyperpolyemric hemoglobin obtained were well fractionable in ultrafiltration (see page 290). Given that the method utilized for cross-linking is the for both the reference and the instant application and given that the purification procedure utilizes the same purification gel and the same buffer, the molecular weight achieved would necessarily be between (5-10) x 100 times the size of native hemoglobin. The difference between the prior art and the instant application is the reference does not teach the exact concentration of S-400 buffers claimed for NaN_3.

However, the MPEP, 2144.05, states "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie
obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.)." Here, the conentration utilized by Applicant of NaN_3 is 1.5 mmol/L. This concentration has not been disclosed to be critical in the specification. Where, it is "apparent that the claimed process is merely different in degree and not in kind from the reference process, and that the criticality of the claimed ranges has not been shown" the change will not support patentability. Aller, 220 F.2d at 459.

Claims 6-9 and 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Potzschke et al. in view of Bonhard et al.

The reference of Potzschke et al. has been discussed supra. The difference between the prior art and the instant application is the Pozschke et al. does not tech the use of Ammonium Sulfate.

However, the reference of Bonhard et al. teaches a method of cross-linking the hemoglobin solution and then diminishing the amount of uncross-linked hemoglobin by the use of Ammonium Sulfate solution (see col. 3, lines 25-35). The crosslinked hemoglobin can be separated from the uncrosslinked hemoglobin because the ammonium sulfate salts out the crosslinked hemoglobin. (see col. 3, lines 29-30). It should be noted that the reference states that the crosslinking agent can be glutaric dialdehyde, the same crosslinking agent used in the Potzschke et al. Therefore it would have been obvious to one of ordinary skill in the art to use ammonium sulfate solution because this solution would separate uncrosslinked-hemoglobin remaining and thus obtaining a purer crosslinked product.

As to the specific concentrations claimed, generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller , *supra.* Here, the reference states that ammonium sulfate was added to the solution for about 17 minutes to separate uncrosslinked hemoglobin from crosslinked hemoglobin (see col. 6, lines 20-24 in Bonhard). It would have been obvious to optimize the time period to find the optimum time frame to achieve total separation of crosslinked hemoglobin from uncrosslinked hemoglobin.

(11) Response to Argument

Before addressing Appellants' arguments, it is assumed that for both rejections, Claims 6-9 and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Potzschke et al. and Claims 11 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Potzschke et al., Appellants' make similar argument that are cited under "Claims 6-14 [sic] and 16 [sic] were rejected as being read only by the cited prior art Poetszschke and Barnikol..." As such, for both rejection, the arguments have been addressed together.

Appellants' argue that Poetzschke describe only an "analytical method" and not a "preparative method" which is the scope of the current claims. Appellants' state that the claims have been "amended to more clearly reflect that the claimed method is a preparative one." The analytical and preparative use of a physiochemical method are not the same. "That a method function on one scale says nothing about the possibility or the ability to scale-up the method. An analytical method merely goes to the ability to detect the distribution of a hydrodynamic molecular weight in a sample, but in no way predicts the ability to separate usable samples." Further, the analytical method leads to small samples that are lost in detection methods, whereas a preparative method must have high yields to survive detection process. "Thus, that one is able to detect the separation of cross-linked hyperpolymeric hemoglobin by its molecular weight, is no guarantee that one can preserve such factions separated by molecular weight."

Appellants' arguments have been considered but are not found persuasive.

Appellants' arguments with respect to analytical method and preparative methods do not have merit because Appellants' have not thoroughly explained how the amended claims are now distinguished over an analytical method. Claim 6 does not make any reference to an "analytical" method or make any reference that such a method is to be excluded from the scope of the claims.

Further, the claims do not make any distinction with respect to the amount of end product obtained. That is, the claims do not state that high yields are desired or low yields should be avoided thereby specifically excluding analytical methods as Appellants' have argued. Moreover, the specification does not make a distinction, via any explicit or implicit language, that analytical methods are excluded from the scope of the invention. Indeed the word "analytical" does not appear in any context that would lead one to conclude that such methods are excluded from the scope of the invention. The MPEP states that the "the pending claims must be "given their broadest reasonable interpretation consistent with the specification." See MPEP 2111. Given the breath of claim 6 and the specification as whole, it is wholly reasonable to conclude that the claim is inclusive of both "preparative" and an "analytical" method. As such, the reference reads on the claimed invention since the reference teaches that the hype polymeric hemoglobin can be purified using Sepharcryl S-400 high-resolution gel.

It is noted that claim 11 uses the word "preparative." Appellants', in their arguments, made the implication that "preparative" methods were distinguishable over analytical methods. However, the use of this word alone does not signify that analytical methods are excluded from the claims. Preparative, utilizing a dictionary definition, is defined as serving or tending to put together or make by combining various elements or ingredients. See Webster's II New riverside University Dictionary, (Anne H. Soukhanov ed., Riverside Publishing Co. 1988). This definition does not imply that analytical methods of preparation be excluded. In fact, analytical methods are also preparative methods because such methods involve the putting together and make by combining various elements or ingredients. Accordingly, one cannot conclude that the presence of the word "preparative," implicates the exclusion of analytical methods from the scope of the claims. Since

such a conclusion cannot be supported, the reference Potzschke et al. anticipate and render obvious the claimed invention.

Appellants' arguments with respect to "Claims 6-16 [sic] were rejected as being unpatentable over Potzschke in view of U.S. Patent 4,136,093 (Bonhard)."

Appellants' make similar arguments for Potezschke as cited above. These arguments have discussed supra and incorporated herein. For Bonhard et al., Appellants' acknowledge that ammonium sulfate is useful to separate out from cross-linked hemoglobin and non-cross-linked hemoglobin and such a teaching is "true." However, Appellants' state that Bonhard does not teach the claimed method of using ammonium sulfate to separate cross-linked hemoglobin from cross-linked hemoglobin with a small molecular weight. Appellants's argue that a rejection does not provide "suggestion, incentive or motivation in either Potzche [sic] or Bonhard for the combination on which the claims were rejected." Appellants' argue that rejection has not presented any "evidence, preferably in the form of some teaching, suggestion incentive or inference in the prior art, or in the form of generally available knowledge, that one having ordinary skill in the art would have been led to combine the relevant teaching."

Appellants' arguments have been considered but have not been found persuasive.

As indicated above, Appellants' acknowledge that "one would expect the non-cross-linked hemoglobin to separate out form the cross-linked hemoglobin as taught in Bonhard" when ammonium sulfate is applied to the sample as "true." This teaching in Bonhard is the "teaching, suggestion incentive or inference in the prior art. . .that one having ordinary skill in the art would have been led to combine the relevant teaching." Potezschke et al. teach the crosslinking of hemoglobin using glutaraldehyde. Since the final product desired in Potezschke et al. is a

crosslinked product, one would be motivated to use a means for removing any uncrosslinked product. Bonhard provides this motivation since it teaches the use of ammonium sulfate to separate crosslinked hemoglobin from non-crosslinked hemoglobin (see col. 3, lines 25-35). Further, Bonhard utilizes glutaraldehyde as on of its crosslinking agent. Given that the same crosslinking agent is used in both references, one would expect that ammonium sulfate would separate the non-crosslinked product from the crosslinked product.

Appellants' imply that the reference does not provide the same motivation as current claims and therefore does not teach nor suggest the claimed invention. However, the MPEP states:

> "The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991) (discussed below). Although Ex parte Levengood, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993) states that obviousness cannot be established by combining references "without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done" (emphasis added), reading the quotation in context it is clear that while there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention." MPEP 2144.

Thus, the fact that Bonhard does not the use ammonium sulfate to separate cross-linked hemoglobin from cross-linked hemoglobin with a small molecular weight is not dispositive of a prima facie case. The requirement to establish a prima facie case of obviousness requires that there be some motivation to make the claimed invention, not the same motivation to make the claimed invention. Here, the Bonhard reference teaches the use of ammonium sulfate to separate non-crosslinked hemoglobin from glutaraldehyde crosslinked hemoglobin. Since the final product is a crosslinked product, one would be motivate to separate the non-crosslinked product using ammonium sulfate, to achieve a purer crosslinked product.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

1/22/04

Anish Gupta

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January 22, 2004

Conferees

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